This listing of claims will replace all prior versions, and listings, of claims in the application:

**LISTING OF CLAIMS:**

1. **(Previously Presented)** A N-deacetylated N-sulfated derivative of K5 polysaccharide, epimerised at least to 40% of iduronic acid with respect to the total uronic acids, having a molecular weight of from 2,000 to 30,000 D, a content in chains with high affinity for ATIII of from 25% to 50% by weight and an anticoagulant and antithrombotic activity expressed as ratio HCII/Anti-Xa between 1.5 and 4.

2. **(Original)** Derivatives according to claim 1 wherein the molecular weight is between 4,000 and 8,000 D.

3. **(Original)** Derivatives according to claim 1 wherein the molecular weight is between 18,000 and 30,000 D.

4. **(Currently Amended)** A process for the preparation of derivatives of K5 polysaccharide as defined in claim 1, comprising in sequence (a) the preparation of K5 polysaccharide from Escherichia coli [Escherichia Coli], (b) N-deacetylation and N-sulfation, (c) C5 epimerization of D-glucuronic acid to L-iduronic acid, (d) oversulfation, (e) selective O-desulfation, (f) selective 6-O-sulfation [6-O sulfation] and (g) N-sulfation, wherein said C5 epimerization is performed using the enzyme glucuronosyl C5 epimerase in solution or in immobilized form in the presence of divalent cations.

5. **(Original)** A process according to claim 4 wherein said enzyme comprises recombinant glucuronosyl C5 epimerase, glucuronosyl C5 epimerase from murine mastocytoma or glucuronosyl C5 epimerase extracted from bovine liver.

6. **(Original)** A process according to claim 4 wherein said divalent cations comprise at least one of Ba, Ca, Mg and Mn.

**7. (Original)** A process according to claim 4 wherein that said C5 epimerization is conducted with the enzyme in solution by dissolving an amount of enzyme C5 epimerase comprised between $1.2 \times 10^7$ and $1.2 \times 10^{11}$cpm in 2-2,000 ml of 25 mM Hepes buffer at a pH between 5.5 and 7.4 containing from 0.001 to 10 g of N-deacetylated N-sulfated K5 and one or a combination of said cations at a concentration comprised between 10 and 60 mM.

**8. (Original)** A process according to claim 7 wherein said C5 epimerization with the enzyme in solution is performed at a temperature between 30 and 40°C for a time comprised between 1 and 24 hours.

**9. (Original)** A process according to claim 4 wherein said C5 epimerization with the enzyme in its immobilized form is performed and comprises recirculating 20-1,000 ml of a solution of 25 mM Hepes at pH from 6 to 7.4 containing 0.001-10 g of N-deacetylated N-sulfated K5 and one of said cations at a concentration between 10 and 60 mM through a column containing from $1.2 \times 10^7$ to $3 \times 10^{11}$cpm of the immobilized enzyme on an inert support.

**10. (Original)** A process according to claim 9 wherein said C5 epimerization is performed at a temperature between 30 and 40°C recirculating said solution with a flow rate of 30-160 ml/hour for a time between 1 and 24 hours.

**11. (Currently Amended)** A process according to claim 4 wherein said selective O-desulfation step (e) is carried out by reacting a tertiary amine or quaternary ammonium salt of the oversulfated product with a solution dimethyl sulfoxide/methanol 9/1 (V/V) at 60°C for 3 hours.

**12. (Currently Amended)** A process according to claim 4 wherein said C5 epimerization of step (c) is performed using the enzyme glucuronosyl C5 epimerase in solution or in immobilized form in presence of divalent cations, said selective O-desulfation of step (e) is carried out by reacting a tertiary or quaternary ammonium salt of the

oversulfated product with a solution dimethyl sulfoxide/methanol 9/1 (V/V) at 60°C for 3 hours and said selective [O-sulfation] 6-O-sulfation of step (f) is performed by reacting a tertiary amine or quaternary ammonium salt of the selectively O-desulfated product with a calculated amount of a sulfating agent at a temperature of 0-5°C for 0.5-3 hours.

**13. (Currently Amended)** A process according to claim 12 wherein said selective [O-sulfation] 6-O-sulfation of step (f) is carried out for 1.5 hours using a pyridine sulfur trioxide adduct as sulfating agent.

**14. (Original)** A process for the preparation of K5 glycosaminoglycans comprising the steps of (i) N-deacetylation/N-sulfation of the polysaccharide K5, (ii) partial C5-epimerization of the carboxyl group of the glucuronic acid moiety to the corresponding iduronic acid moiety, (iii) oversulfation, (iv) selective O-desulfation, (v) optional 6-O-sulfation, and (vi) N-sulfation, in which step (iv) comprises treating the oversulfated product obtained at the end of step (iii) with a mixture methanol/dimethyl sulfoxide for a period of time of from 135 to 165 minutes.

**15. (Original)** A process according to claim 14 in which said period of time is of about 150 minutes.

**16. (Original)** A process according to claim 14 in which said treatment is made for a period of time of about 150 minutes at a temperature of about 60°C.

**17. (Previously Presented)** A process for the preparation of novel glycosaminoglycans, which comprises

(i) reacting polysaccharide K5 with a N-deacetylating agent, then treating the N-deacetylated product with a N-sulfating agent;

(ii) submitting the N-sulfate K5 thus obtained to a C5-epimerization by glucuronosyl C5 epimerase to obtain a C5-epimerized N-sulfate K5 in which the iduronic/glucuronic ratio is from 60/40 to 40/60;

(iii) converting the C5 epimerized N-sulfate K5, having a content of 40 to 60% iduronic acid over the total uronic acids, into a tertiary amine or quaternary ammonium salt thereof, then treating the salt thus obtained with an O-sulfating agent in an aprotic polar solvent at a temperature of 40-60°C for 10-20 hours;

(iv) treating an organic base salt of the O-oversulfated product thus obtained with a mixture dimethyl sulfoxide/methanol at 50-70 °C for 135-165 minutes to perform a partial O-desulfation;

(v) treating an organic base salt of the partially O-desulfated product thus obtained with an O-sulfating agent at a temperature of 0-5°C to perform a 6-O-sulfation;

(vi) treating the O-sulfated product thus obtained with a N-sulfating agent;

whatever product obtained at the end of one of steps (ii) to (vi) being optionally submitted to a depolymerization.

**18. (Original)** A process according to claim 17, wherein a previously purified K5 is used as starting material.

**19. (Original)** A process according to claim 17, wherein, in step (i), hydrazine or a salt thereof or an alkaline metal hydroxide is used as a N-deacetylating agent and pyridine.sulfur trioxide or trimethylamine.sulfur trioxide adduct is used as a N-sulfating agent.

**20. (Original)** A process according to claim 17 wherein, in step (ii), said C5 epimerization is performed using the enzyme glucuronosyl C5 epimerase in solution or in immobilized form in presence of divalent cations.

**21. (Original)** A process according to claim 20 wherein said divalent cations comprise at least one of Ba, Ca, Mg and Mn.

**22. (Previously Presented)** A process according to claim 17, wherein, in step (ii), said epimerase is selected from the group consisting of recombinant glucuronosyl C5 epimerase, glucuronosyl C5 epimerase from murine mastocytoma and glucuronosyl C5 epimerase extracted from bovine liver.

**23. (Original)** A process according to claim 20 wherein said C5 epimerization with the enzyme in its immobilized form is performed and comprises recirculating 20-1,000 ml of a solution of 25 mM Hepes at pH of from 6 to 7.4 containing 0.001-10 g of N-deacetylated N-sulfated K5 and one of said cations at a concentration between 10 and 60 mM through a column containing from $1.2 \times 10^7$ to $3 \times 10^{11}$cpm of the immobilized enzyme on an inert support.

**24. (Original)** A process according to claim 23 wherein said pH is of about 7 and said C5 epimerization is performed with a recombinant enzyme at a temperature of about 30°C by recirculating said solution with a flow rate of from 30 to 220 ml/hour for a time of about 24 hours.

**25. (Original)** A process according to claim 17, wherein, in step (iii), the pyridine.sulfur trioxide adduct is used as O-sulfating agent.

**26. (Original)** A process according to claim 17, wherein, in step (iv), the reaction is carried out in dimethyl sulfoxide/methanol 9/1 (V/V) at about 60°C for about 150 minutes.

**27. (Original)** A process according to claim 17, wherein a previously purified K5 is used as starting material and, in step (iv), the reaction is carried out in dimethyl sulfoxide/methanol 9/1 (V/V) at about 60°C for about 150 minutes.

**28. (Original)** A process according to claim 17, wherein, in step (v), the 6-O-sulfation is carried out at 0-5°C by using the pyridine.sulfur trioxide adduct as O-sulfating agent.

**29. (Original)** A process according to claim 17, wherein, in step (vi), pyridine.sulfur trioxide or trimethylamine.sulfur trioxide adduct is used as N-sulfating agent.

**30. (Original)** A process according to claim 17, wherein the product obtained at the end of step (vi) is submitted to a nitrous acid depolymerization followed by a reduction by sodium borohydride.

**31. (Original)** A process according to claim 17, wherein a previously purified K5 is used as starting material and, in step (iv), the reaction is carried out in dimethyl sulfoxide/methanol 9/1 (V/V) at about 60°C for about 150 minutes, and the C5-epimerized N,O-sulfate K5 glycosaminoglycan obtained at the end of step (vi) is submitted to a nitrous acid depolymerization followed by a reduction by sodium borohydride.

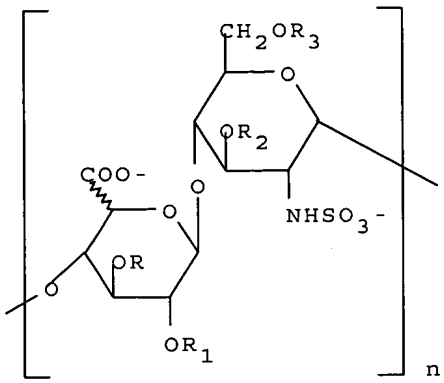
**32. (Original)** A process according to claim 17, wherein the glycosaminoglycan thus obtained is isolated in form of its sodium salt.

**33. (Previously Presented)** A process according to claim 32, wherein said sodium salt is further converted into another salt of said glycosaminoglycan.

**34. (Previously Presented)** A process according to claim 33, wherein said other salt is another alkaline metal, or an alkaline-earth metal, ammonium, tetra($C_1$-$C_4$)alkylammonium, aluminium or zinc salt.

**35.–37. (Canceled)**

**38. (Original)** A glycosaminoglycan constituted by a mixture of chains in which at least 90% of said chains has the formula I

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wherein 40-60% of the uronic acid units are those of iduronic acid, n is an integer from 3 to 100, R, $R_1$, $R_2$ and $R_3$ represent a hydrogen atom or a $SO_3^-$ group and from about 65% to about 50% of R, $R_1$, $R_2$ and $R_3$ being hydrogen and the remaining being $SO_3^-$ groups distributed as follows

- $R_3$ is from about 85% to about 95% $SO_3^-$;
- $R_2$ is from about 17 to about 21% $SO_3^-$;
- $R_1$ is from about 15 to about 35% $SO_3^-$ in iduronic units and 0 to 5% $SO_3^-$ in glucuronic units;
- R is from about 20 to about 40% $SO_3^-$ in glucuronic units and 0 to 5% in iduronic units;
- the sum of the $SO_3^-$ percent in $R_1$, glucuronic units, and in R, iduronic units, is from 3 to 7%;

$R_1$ and R being not simultaneously $SO_3^-$ and being both hydrogen in 25-45% of the uronic acid units; the sulfation degree being from about 2.3 to about 2.9, and the corresponding cation being a chemically or pharmaceutically acceptable one.

**39. (Original)** The glycosaminoglycan of claim 38 wherein said corresponding cation is an alkaline metal, alkaline-earth metal, aluminum or zinc ion.

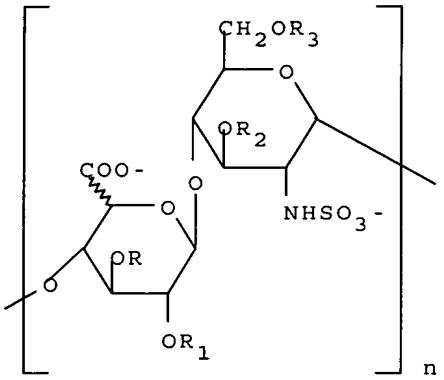
**40. (Original)** The glycosaminoglycan of claim 38 wherein said corresponding cation is sodium or calcium ion.

**41. (Previously Presented)** The glycosaminoglycan of claim 38 wherein from about 60% to about 55% of R, $R_1$, $R_2$ and $R_3$, taken together, are hydrogen and the remaining are $SO_3^-$ groups for a sulfation degree of from about 2.4 to about 2.7.

**42. (Original)** The glycosaminoglycan of claim 38 wherein at least 80% of said chains in said mixture of chains have the formula I wherein n is from 3 to 15.

**43. (Original)** The glycosaminoglycan of claim 42 wherein said chains in said mixture of chains has a molecular weight distribution ranging from about 2,000 to about 10,000, with a mean molecular weight of from about 4,000 to about 8,000.

**44. (Original)** The glycosaminoglycan of claim 43 wherein said chains in said mixture of chains have a mean molecular weight of about 7,000 and at least 90% of said mixture of chains has the formula I,




(I)

wherein about 55% of the uronic acid units are those of iduronic acid and

- $R_3$ is about 85% $SO_3^-$;
- $R_2$ is about 20% $SO_3^-$;
- $R_1$ is about 25% $SO_3^-$ in iduronic units and 0 to about 5% $SO_3^-$ in glucuronic units;
- R is about 30% $SO_3^-$ in glucuronic units and 0 to about 5% in iduronic units;
- the sum of the $SO_3^-$ percent in $R_1$, glucuronic units and in R, iduronic units, is about 5%;

$R_1$ and R being not simultaneously $SO_3^-$ and being both hydrogen in about 40% of the uronic acid units; the sulfation degree being about 2.55, the corresponding cation being a chemically or pharmaceutically acceptable one.

**45. (Original)** The glycosaminoglycan of claim 44 wherein said corresponding cation is an alkaline metal, alkaline-earth metal, aluminum or zinc ion.

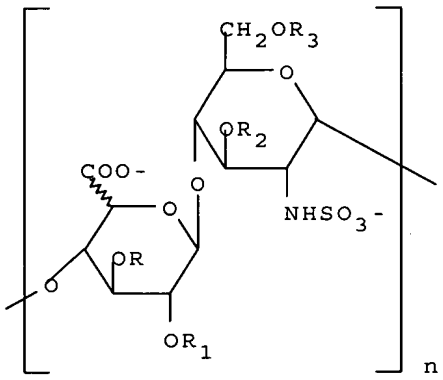
**46. (Original)** The glycosaminoglycan of claim 44 wherein said corresponding cation is sodium or calcium ion.

**47. (Original)** The glycosaminoglycan of claim 44, wherein said mixture of chains has a mean molecular weight of 7,400.

**48. (Original)** The glycosaminoglycan of claim 38 wherein at least 80% of said chains in said mixture of chains have the structure I wherein n is from 20 to 100.

**49. (Original)** The glycosaminoglycan of claim 48 wherein said mixture of chains has a molecular weight distribution ranging from about 9,000 to about 60,000, with a mean molecular weight of from about 12,000 to about 30,000 .

**50. (Previously Presented)** The glycosaminoglycan of claim 49 wherein said chains in said mixture of chains have a mean molecular weight of 14,000-16,000 and at least 90% of said chains have the formula I,

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wherein about 55% of the uronic acid units are those of iduronic acid and

- $R_3$ is from about 85% to about 90% $SO_3^-$;
- $R_2$ is about 20% $SO_3^-$;
- $R_1$ is from about 25% to about 30 $SO_3^-$ in iduronic units and 0 to about 5% $SO_3^-$ in glucuronic units;
- R is from about 30% to about 35% $SO_3^-$ in glucuronic units and 0 to about 5% in iduronic units;

- the sum of the $SO_3^-$ percent in R1, glucuronic units and in R, iduronic units, is about 5%; $R_1$ and R being not simultaneously $SO_3^-$ and being both hydrogen in from about 30% to about 40% of the uronic acid units; the sulfation degree being from about 2.5 to about 2.7, the corresponding cation being a chemically or pharmaceutically acceptable one.

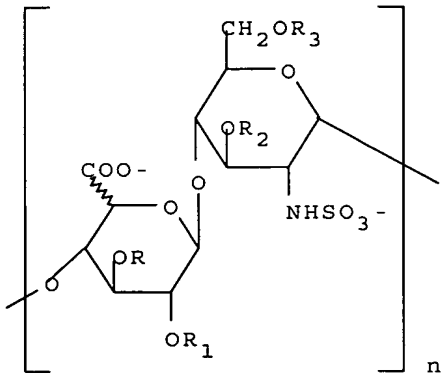
**51. (Original)** The glycosaminoglycan of claim 50 wherein said corresponding cation is an alkaline metal, alkaline-earth metal, aluminum or zinc ion.

**52. (Original)** The glycosaminoglycan of claim 50 wherein said corresponding cation is sodium or calcium ion.

**53. (Original)** The glycosaminoglycan of claim 50, wherein said mixture of chains has a mean molecular weight of 15,700.

**54.–55. (Canceled)**

**56. (Original)** A pharmaceutical composition comprising a pharmacologically effective amount of a glycosaminoglycan constituted by a mixture of chains in which at least 90% of said chains has the formula I

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wherein 40-60% of the uronic acid units are those of iduronic acid, n is an integer from 3 to 100, R, $R_1$, $R_2$ and $R_3$ represent a hydrogen atom or a $SO_3^-$ group and from about 65% to about 50% of R, $R_1$, $R_2$ and $R_3$ being hydrogen and the remaining being $SO_3^-$ groups distributed as follows

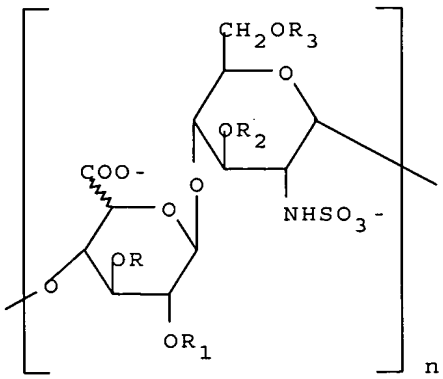
- $R_3$ is from about 85% to about 95% $SO_3^-$;
- $R_2$ is from about 17 to about 21% $SO_3^-$;
- $R_1$ is from about 15 to about 35% $SO_3^-$ in iduronic units and 0 to 5% $SO_3^-$ in glucuronic units;
- R is from about 20 to about 40% $SO_3^-$ in glucuronic units and 0 to 5% in iduronic units;
- the sum of the $SO_3^-$ percent in R1, glucuronic units, and in R, iduronic units, is from 3 to 7%;

$R_1$ and R being not simultaneously $SO_3^-$ and being both hydrogen in 25-45% of the uronic acid units; the sulfation degree being from about 2.3 to about 2.9, and the corresponding cation being a pharmaceutically acceptable one, as an active ingredient, and a pharmaceutically acceptable carrier.

**57. (Original)** The composition of claim 56 wherein said glycosaminoglycan is constituted by a mixture of chains in which at least 80% of said chains have the formula I, in which n is from 3 to 15.

**58. (Original)** The composition of claim 57 wherein said mixture of chains has a molecular weight distribution ranging from about 2,000 to about 10,000 with a mean molecular weight of from about 4,000 to about 8,000.

**59. (Original)** The composition of claim 58 wherein said mixture of chains has a mean molecular weight of about 7,000 and at least 90% of said chains has the formula I

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wherein about 55% of the uronic acid units are those of iduronic acid and

- $R_3$ is about 85% $SO_3^-$;
- $R_2$ is about 20% $SO_3^-$;
- $R_1$ is about 25% $SO_3^-$ in iduronic units and 0 to about 5% $SO_3^-$ in glucuronic units;
- R is about 30% $SO_3^-$ in glucuronic units and 0 to about 5% in iduronic units;
- the sum of the $SO_3^-$ percent in $R_1$, glucuronic units, and in R, iduronic units, is about 5%;

$R_1$ and R being not simultaneously $SO_3^-$ and being both hydrogen in about 40% of the uronic acid units; the sulfation degree being about 2.55, the corresponding cation being a pharmaceutically acceptable one.

**60. (Original)** The composition of claim 59 wherein said corresponding cation is an alkaline metal, alkaline-earth metal, aluminium or zinc ion.

**61. (Original)** The composition of claim 59 wherein said corresponding cation is sodium or calcium ion.

**62. (Original)** The composition of claim 59 wherein said mixture of chains has a mean molecular weight of 7,400.

**63. (Original)** A method for controlling coagulation in a mammal, which comprises administering to said mammal, in need of said coagulation control, a pharmacologically effective amount of the C5-epimerized N,O-sulfate K5 glycosaminoglycan of claim 35.

**64. (Original)** A method for controlling coagulation in a mammal, which comprises administering to said mammal, in need of said coagulation control, a pharmacologically effective amount of the glycosaminoglycan of claim 38.

**65. (Original)** A method for preventing or treating thrombosis in a mammal which comprises administering to said mammal an effective amount of the C5-epimerized N,O-sulfate K5 glycosaminoglycan of claim 35.

**66. (Original)** A method for preventing or treating thrombosis in a mammal which comprises administering to said mammal an effective amount of the glycosaminoglycan of claim 38.

**67. (Original)** The method of claim 63 wherein said effective amount is administered in a pharmaceutical composition containing from 5 to 100 mg of said glycosaminoglycan.

**68. (Original)** The method of claim 64 wherein said effective amount is administered in a pharmaceutical composition containing from 5 to100 mg of said glycosaminoglycan.

**69. (Original)** The method of claim 65 wherein said effective amount is administered in a pharmaceutical composition containing from 5 to100 mg of said glycosaminoglycan.

**70. (Original)** The method of claim 66 wherein said effective amount is administered in a pharmaceutical composition containing from 5 to100 mg of said glycosaminoglycan.

**71. (New)** A process for the preparation of N-deacetylate N-sulfate derivatives of K5 polysaccharide, epimerized at least till 40% of iduronic acid with respect to the total uronic acids, having molecular weight from 2,000 to 30,000 D, containing from 25 to 50% on weight of the chains with high affinity for ATIII and having an anticoagulant and antithrombotic activity expressed as ratio HCII/Anti-Xa comprised between 1.5 and 4, said process comprising in sequence (a) the preparation of K5 polysaccharide from *Escherichia coli*, (b) N-deacetylation and N-sulfation, (c) C5 epimerization of D-glucuronic acid to L-iduronic acid, (d) oversulfation, (e) selective O-desulfation, (f) selective 6-O-sulfation and (g) N-sulfation, wherein

- said C5 epimerization is performed using the enzyme glucuronosyl C5 epimerase in solution or in immobilized form in the presence of divalent cations;

- said oversulfation of step (d) is performed by treating a tertiary amine or quaternary ammonium salt of the C5-epimerized product obtained at the end of step (c) with a sulfating agent at 20-70°C for 2-24 hours to perform an O-oversulfation; and
- said selective O-desulfation of step (e) is performed by treating the N-desulfated and O-oversulfated product obtained at the end of step (d) with a solution of dimethyl sulfoxide/methanol 9/1 (V/V) at 45-90°C for 1-8 hours.

**72.** **(New)** The process of claim 71, wherein in said step (d) said salt of said C5-epimerized product is the tetrabutylammonium salt.

**73.** **(New)** The process of claim 72, wherein in said oversulfation step (d) said sulfating agent is pyridine.$SO_3$.

**74.** **(New)** The process of claim 73, wherein said oversulfation is carried out in dimethyl formamide or dimethyl sulfoxide solution.

**75.** **(New)** The process of claim 71, wherein said 6-O-sulfation of step (f) is performed by treating a tertiary amine or quaternary ammonium salt of the partially O-desulfated product obtained at the end of step (e) with a sulfating agent at 0-5°C for 2-24 hours.

**76.** **(New)** The process of claim 75, wherein in said step (f) said salt of the partially O-desulfated product is the tetrabutylammonium salt.

**77.** **(New)** The process of claim 76, wherein said sulfation is carried out in dimethyl formamide or dimethyl sulfoxide solution.